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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/928,847	08/13/2001	Steen Troels Jorgensen	10022.204-US	9117

25908 7590 12/17/2002

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EXAMINER	
LAMBERTSON, DAVID A	
ART UNIT	PAPER NUMBER

1636
DATE MAILED: 12/17/2002

13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/928,847	JORGENSEN ET AL.
	Examiner David A Lambertson	Art Unit 1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 07 October 2002.
 2a) This action is **FINAL**. 2b) This action is non-final.
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-5,30-44,63 and 66 is/are pending in the application.
 4a) Of the above claim(s) 30-43 and 66 is/are withdrawn from consideration.
 5) Claim(s) _____ is/are allowed.
 6) Claim(s) 1-5,44 and 63 is/are rejected.
 7) Claim(s) _____ is/are objected to.
 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.
 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.
 If approved, corrected drawings are required in reply to this Office action.
 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
 * See the attached detailed Office action for a list of the certified copies not received.
 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
 a) The translation of the foreign language provisional application has been received.
 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) Notice of References Cited (PTO-892)
 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
 3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) 10.
 4) Interview Summary (PTO-413) Paper No(s). _____.
 5) Notice of Informal Patent Application (PTO-152)
 6) Other: _____

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I in Paper No. 12 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The requirement is still deemed proper and is therefore made FINAL.

Claims 30-43 and 66 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Group, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 12.

Claims 1-5, 44 and 63 are ready for examination in the instant application. Applicant has elected the *dal* and *gale* genes with respect to claim 63.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Denmark on June 23, 2000. It is noted, however, that applicant has not filed a certified copy of the Danish application as required by 35 U.S.C. 119(b). As such, foreign priority to this application has not been granted. Therefore, the priority date of this application is July 13, 2000.

Drawings

Applicant is hereby informed that the Drawings as submitted have been approved by the Draftsperson.

Claim Objections

Claim 63 is objected to because of the following informalities: claim 63 contains non-elected subject matter. Claim 63 has been elected to read on a *Bacillus licheniformis* cell where both *dal* and *galE* are rendered non-functional. Claim 63 still contains a number of non-elected “conditionally essential genes”. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 44 and 63 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant claims a method for constructing any cell comprising at least two copies of a gene of interest, where the cell comprises conditionally essential genes. Applicants provide a written description only on the use of *Bacillus* cells containing very specific conditionally

essential genes. Applicant's claims read on a broad genus of cells containing a broad range of conditionally essential genes.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics sufficient to show applicants were in possession of the claimed genus. In the instant case, it is unclear from the specification what genes can be made conditionally essential, and in what cells these conditionally essential genes can be made/are present. Therefore, the specification does not disclose a critical element of the claimed invention.

Applicant claims a method for constructing cells having conditionally essential genes by function only, without any disclosed or known correlation between the elements and their function. There are a large number of genes in every cell type, and it is unclear from the instant specification what genes can be mutated to be conditionally essential in each of these cell types. Furthermore, it is unclear that higher eukaryotic cells can be mutated to develop conditionally essential phenotypes. The specification only provides teachings regarding the use of *Bacillus* cells having specific conditionally essential genes (e.g. *galE*, *dal*, etc.). Even in the instance of claim 63, where the claim reads on genes that are "preferably" used, the specification has not provided a sufficient written description because it is unclear what other genes from the many genes found in *B. licheniformis* can be mutated to be conditionally essential. The skilled artisan cannot envision a sufficient number of embodiments of the instant invention from the instant

specification because the specification describe what genes in other types of cells can be made to be conditionally essential.

The prior art does not provide sufficient information on the subject to overcome the written description requirements. There is no description in the prior art that allows one to envision a representative number of cells that can be used in the invention by disclosing what genes can be mutated into conditionally essential genes. It is also not apparent from the prior art that the method would function similarly in all types of cells, such as higher eukaryotic cells, because it is unclear that these cells can be generated to contain conditionally essential genes. Thus the skilled artisan cannot rely on the prior art to envision a sufficient number of embodiments of the instant invention to conclude that the applicant was in possession of the claimed genus.

Neither the specification of the instant application or the prior art teaches a representative number of cells that can be used in the instant invention. As a result, the skilled artisan would not be able to envision the claimed invention by relying on the teachings of the prior art or the instant specification. Therefore applicant has not satisfied the written description requirement to show the skilled artisan that they were in possession of the claimed genus.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5, 44 and 63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 2 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: a step referring to the recombination event that results in the restoration of the conditionally essential gene.

Claims 1 and 2 are rejected because the claim refers to "an altered non-functional copy of the conditionally essential gene" in section (b) part (i) of the claim. It would be remedial to indicate either that the non-functional copy of the gene is being altered, or that the functional or conditionally essential copy of the gene is being rendered non-functional.

The term "adjacent" in claims 1 and 2 is a relative term which renders the claim indefinite. The term "adjacent" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is unclear how close the gene of interest must be to the conditionally essential gene in the host chromosome in order for the genes to be adjacent, therefore the claim language fails to define the metes and bounds of the invention as claimed.

Claim 1 recites the limitation "genes of step (a)" in lines 11, 12, 19 and 20 of the claim. There is insufficient antecedent basis for this limitation in the claim. Step (a) mentions two chromosomal genes, the gene of interest and the conditionally essential gene. It would be remedial to amend the claim language to clearly indicate which of the possible genes is referred to by the words "genes of step (a)" at each point in the claim.

Regarding claim 63, the phrase "for example" (the interpreted meaning for preferably) renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2 and 44 are rejected under 35 U.S.C. 102(b) as being anticipated by De Groot et al. (WO'99/32641; see entire document).

WO 99/32641 describes a method of stably introducing multiple copies of a desired gene into a host cell chromosome by site-directed recombination without the use of antibiotic markers, where the specific site-directed recombination event is selected for by the restoration of a selectable marker (see for example pages 7-8, line 34-10). Specifically, the selectable markers can be those genes which are characteristically present in the wild-type strain, but are absent in the host cell to be transformed, and include auxotrophic markers as well as genes that are easily assayable (see for example page 13, lines 12-27). The desired locus for the recombination event is preferably within the selectable marker (see for example page 13, lines 30-31), thereby allowing the direct selection of events that result in the integration of the target gene. The specification also refers to another integrative procedure for inserting multiple copies of a target gene into the chromosome by repeating a single copy site-directed mutagenesis step at multiple

sites (pages 5-6, lines 31-2). The use of different selectable markers by the specification in light of this disclosure suggests that the use of multiple different selection markers would allow for a repeat of the integration at different locations in the chromosome to increase the number of copies of target gene in the host cell. The specification also inherently refers to host cells that can be used in the method by including them in the process.

Allowable Subject Matter

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A Lambertson whose telephone number is (703) 308-8365. The examiner can normally be reached on 8am-4:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

David A. Lambertson
PATENT EXAMINER

David A. Lambertson
December 16, 2002